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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/458,779	12/10/1999	MARTIN LATTERICH	1211.001US1	9268

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EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/458,779	Applicant(s) LATTERICH ET AL.	
	Examiner David A Lambertson	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-12,14-23,25-27,29-34,36-42 and 47-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-12,14-23,25-27,29-34,36-42 and 47-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on October 2, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/458779 is acceptable and a CPA has been established. An action on the CPA follows.

Receipt is acknowledged of a reply, filed October 2, 2002 as Paper Nos. 17-21, to the previous Office Action. Amendments were made to the claims.

Claims 3-12, 14-23, 25-27, 29-34, 36-42 and 47-52 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, Paper No. 16, mailed March 26, 2002, that is not addressed in this action has been withdrawn. The declaration filed on October 2, 2002 (Paper No. 18) under 37 CFR 1.131 is sufficient to overcome the Powell, *et al.* reference.

Information Disclosure Statement

The information disclosure statement filed October 10, 2002 as Paper No. 17 has been considered.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 3-7, 11 and 12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a polynucleotide sequence. The

"hand of man" is absent in the invention as claimed. Indication that the polynucleotide is isolated would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 5-12, 14, 16-23, 25, 31-34, 36-42 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims polynucleotides, polypeptides, expression vectors and host cells comprising "conservative variations" of the Vff2 protein represented by SEQ ID NO: 2. The claims read on a broad genus of proteins that can be encoded with these variations.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of conservative variations by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims a "conservative variation" by function only, without any disclosed or known correlation between the elements and their function. The specification only provides teachings concerning the use of the wildtype protein. Although applicant refers to four different groupings of amino acids according to characteristics regarding the side chain of the amino acids (see page 9 starting at line 14 of the instant specification), these groupings do not indicate which of the available changes in the amino acids of the Vff2 protein are allowable without changing the activity of the protein. Furthermore, the amino acid groupings in the instant specification contain amino acids of very different properties (i.e., tryptophan and alanine are considered to be substitutable; however, alanine scanning is often used as a mutational method to obtain functional mutants of a protein). The specification does not teach what amino acid substitutions would retain the function of the Vff2 protein. Therefore the skilled artisan cannot envision a sufficient number of conservative variations of Vff2 from the instant specification because the specification only discloses the use of the wildtype protein.

The prior art does not provide sufficient information on the subject to overcome the written description requirements. The Vff2 protein appears to be novel in terms of the prior art. However, there is no description in the prior art that allows one to envision a representative number of conservative variations of Vff2 by disclosing structural or functional features of the protein so that one of skill in the art could identify amino acids that could be readily substituted, as claimed in the instant invention. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Neither the specification of the instant application or the prior art teaches a structure-function relationship for a representative number of conservative variations of Vff2. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claims 3-12, 14-23, 25-27, 29-34, 36-42 and 47-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the expression of Vff2 protein in secretory mutants for *Saccharomyces cerevisiae* host cells, does not reasonably provide enablement for a useful expression of Vff2 protein in any host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. The invention is the expression of a *Saccharomyces cerevisiae* vesicular fusion protein, Vff2, in various types of host cells for the intended use of increasing the

secretion of heterologous proteins form the host cells, as well as increasing the growth rate of the cells and as a method for screening yeast secretory mutants. The nature of the invention is very unpredictable because the it requires that the Vff2 protein be functional across a number of different species of yeast (as well as across a number of other cell types in instances where the cell is simply referred to as a "host cell"; this can read on any cell type, including mammalian and bacterial cells, for example). A list of references are recited to show that a number of proteins have been shown to be non-functional across species of yeast, and in some cases reasons for this inability to complement are given (see for example the Abstracts of *Gene* **41**:321-325, 1986; *Nuc. Acids. Res.* **22**:200-207, 1994; *Yeast* **14**:409-417, 1998; *Mol. Cell. Biol.* **19**:8461-8468, 1999; *J. Biol. Chem.* **276**:20529-20535, 2001). Because it cannot be predicted if a given protein will be functional across different species of yeast, practicing the invention as claimed in non-*S. cerevisiae* species would be unpredictable. A second point of interest is that on page 16, lines 14-15, the specification indicates that secretory mutants should be selected as host cells for use in the invention. It is unclear from the specification what secretory mutants in non- *S. cerevisiae* cells would be suitable to practice the invention, therefore practicing the invention in non-*S. cerevisiae* cells would be further complicated. The statement indicates that practicing the invention in *S. cerevisiae* cells that are not secretory mutants would be unpredictable, because it is not immediately clear from the prior art or the specification that the invention would work under such circumstances. Finally, although the Vff2 polynucleotide and protein can be expressed in other host cells when using the appropriate promoter sequences, without a predictable demonstration of function, there is no apparent use for the expression of a non-

functional polypeptide in these cells. As such, the invention only has an enabled use when practiced with secretory mutants for *S. cerevisiae* cells.

Scope of the invention. The scope of the invention is very broad, claiming the expression and use of the Vff2 sequences in a number of host cells, ranging specifically from a variety of a species of yeast (e.g., claim12), to any host cell type, including non-yeast cells (e.g., claim 7). The specification only provides an enabled use when practiced with *S. cerevisiae* cells, for reasons made of record in the **Nature of the invention** section of this rejection. The specification further states that these cells should be secretory mutants, but the scope of the claims encompasses the use of wildtype yeast, and it is not immediately clear from the specification that these cells are enabled within the scope of the invention.

State of the art. The prior art does not disclose the use of Vff2 proteins for the increased secretion of proteins from host cells, thus the invention appears to be novel in terms of the prior art. However, the lack of support from the prior art for the use of Vff2 proteins across different host cells results in the invention being unpredictable in terms of its use in non-*S. cerevisiae* cells. Furthermore, there is an absence of direction concerning the use of appropriate secretory mutants in non-*S. cerevisiae* cells when practicing the invention as well as the use of *S. cerevisiae* cells that do not harbor secretory mutations. In the absence of guidance from the prior art, the skilled artisan would be required to practice unpredictable and undue trial and error experimentation when practicing the invention in host cells that are not secretory mutants of *S. cerevisiae*.

Number of working examples and Guidance provided by applicant. The instant specification only provides guidance and working examples concerning the use of the Vff2

protein in *S. cerevisiae* host cells, particularly secretory mutants. Considering the unpredictability surrounding the cross-species functionality of proteins pointed out in the **Nature of the invention** section of this rejection, the skilled artisan would have to practice undue and unpredictable trial and error experimentation in order to practice the invention in host cells that are not secretory mutants of *S. cerevisiae*.

Level of skill in the art. The level of skill in the recombinant production of proteins by secretion from yeast species is high. However, the functional use of proteins from different species is very underdeveloped, particularly with regard to the use of the Vff2 protein in non- *S. cerevisiae* secretory mutant host cells.

Unpredictability of the art. There are a number of examples of proteins (as recited in the Nature of the invention section) that cannot function in different species of yeast. Both the prior art and the instant specification are deficient in terms of teaching that the Vff2 protein is a protein that can be used across different yeast species. A second point of unpredictability regards the use of secretory mutants in non-*S. cerevisiae* cells as it is unclear which mutants would be appropriate for practicing the invention. In light of these deficiencies, the skilled artisan would be forced to practice undue and unpredictable trial and error experimentation when practicing the instant invention.

Amount of experimentation required. Considering the Nature of the invention, the guidance provided by both the prior art and the instant specification, and the broad scope of the invention, it is clear that the skilled artisan would be required to practice undue and unpredictable trial and error experimentation to practice the invention within the scope that it is claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 8-10, 16, 19-21 and 47-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites "A polynucleotide...wherein the protein is about 32 kD" and claim 16 recites "An expression vector... wherein the protein is about 32 kD". Both claims refer to a protein, but the preamble is directed to a non-protein invention. Changing the claim to read "encoded" or "expressed" prior to protein would be remedial.

Claims 8-10, 19-21 and 42 are indefinite because the claims recite a polynucleotide according to SEQ ID NO: 1 further comprising a sequence encoding a heterologous target protein. Are the sequences linked so as to form a fusion protein of Vff2 and the target protein, or is applicant intending to indicate that the two proteins are separate from each other? It is unclear what the relationship is between the polynucleotide of SEQ ID NO: 2 and the polynucleotide encoding the heterologous target protein. Indication that the sequences are operably linked (if they are) or that the polynucleotides are expressed as independent molecules (e.g., not in the form of a fusion protein), would be remedial.

Claims 47-52 recite that the "protein increases *S. cerevisiae* cell growth or protein expression". It appears that the applicant has interchanged "expression" for "secretion".

Response to Arguments Concerning Claim Rejections Under 35 USC § 112

Applicant's arguments filed October 2, 2002 have been fully considered but they are not persuasive.

Written Description

Applicant has argued the following points:

1. That literature regarding conservative variation can be found throughout the specification.
2. That methods of detecting whether a protein can increase yeast cell growth or protein secretion are provided.

In response, although the specification describes what types of amino acid changes can be considered to be conservative variations, the specification does not teach what portions of the Vff2 protein can be changed without a loss of activity. Without an identification of the regions that are essential for maintaining the activity of Vff2p, the skilled artisan would have no way of envisioning what conservative mutations could be made in the protein. Additionally, methods of detecting whether a protein can increase yeast cell growth or protein secretion does not describe what regions of the Vff2p can be changed without a loss in activity. This argument actually addresses possible enablement questions regarding conservative mutations of the Vff2p, and does not address the written description issues.

In conclusion, the arguments made in the response are not sufficient to overcome the 112 first paragraph rejections concerning the written description requirement.

Enablement

Applicant has argued the following points:

1. That the field of yeast genetics is well understood and that procedures for making recombinant products using yeast have been known for years.

2. That a specification need not provide examples of all embodiments of the invention in order to satisfy the enablement requirement.

3. That a claim may encompass the use of a polynucleotide in a number of species without raising enablement issues.

4. That in light of the 3 arguments above, the skilled artisan would have a reasonable expectation of success in using the invention in multiple yeast species.

In response, it is clear that yeast genetics has been understood and practiced for years. However, it is also clear that not all yeast proteins are functional upon expression across species of yeast (see references cited in the aforementioned enablement rejections). Therefore, the facts that the specification need not provide an example for embodiments of functional expression across species and that the claims do not necessarily raise enablement issues simply because they recite a use across species are not applicable due to the unpredictability of the claimed invention. As such, the skilled artisan would not have a reasonable expectation of success in light of the unpredictability of the invention.

In conclusion, the arguments as presented are not sufficient to overcome the issues concerning the 112 first paragraph rejections based on a lack of an enabled disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3-7, 11, 36, 47 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by EMBL entry SCL9476.

EMBL:SCL9476 discloses the full sequence of chromosome IV from *S. cerevisiae* in the form of cosmid 9476. One of the sequences on the chromosome is identified as YDR361c (see entry S0002769 on page 16 of the attached sequence entry), which is 100% identical to SEQ ID NO: 1 and translates into a protein that is 100% identical to SEQ ID NO: 2. Since the encoded proteins are identical, the protein must necessarily be about 32 kD. This sequence contains the natural promoter for YDR361C which is necessarily active in the host strain. Concerning claims 47-50, the bodies of the claims are merely reciting inherent functions of the protein encoded by the polynucleotides as claimed, therefore the claims are interpreted to read on the isolated polynucleotide, which is anticipated by the sequence disclosed in EMBL:SCL9476.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-18, 22, 23, 25, 26, 29, 49 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over EMBL:SCL9476 in view of Mannhaupt *et al.* (Gene 85: 303-311, 1989; see entire document; henceforth Mannhaupt).

EMBL:SCL9476 teaches a polynucleotide that is 100% identical to SEQ ID NO: 1, encoding a protein that is 100% identical to SEQ ID NO: 2 (see entry S0002769(YDR361c) on page 16 of the attached sequence entry). The reference teaches that the sequence is located on a cosmid clone of *S. cerevisiae* chromosome IV, therefore the cosmid contains the necessary endogenous promoter sequence associated with SEQ ID NO: 1. Since the promoter is endogenous, it must necessarily function in the host organism, *S. cerevisiae*.

EMBL:SCL9476 does not teach the expression of the polynucleotide from the cosmid, or a host cell that has been genetically modified to express the polynucleotide.

Mannhaupt teaches that expression of a yeast gene can be accomplished using a cosmid transformed into a yeast strain. Specifically, Mannhaupt teaches the identification of the *TYR1* gene from yeast by expressing the gene from cosmid clone c922 in an appropriate yeast host cell (see for example page 305, section (b)). Since the assay is measured by complementation of a mutant gene, the gene on the cosmid must necessarily be expressed in the genetically modified host cell.

It would have been obvious to the ordinary skilled artisan to use c9476 for the expression of the YDR361c gene in a yeast strain because it was known in the art at the time of the invention that cosmids could be used for the expression of yeast genes in yeast host cells. The ordinary skilled artisan would have been motivated to use c9476 as an expression vector in a genetically modified yeast in order to identify a function for the YDR361c gene by complementation assay, as described by Mannhaupt. Absent evidence to the contrary and given the teachings of the stated prior art and the high level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Allowable Subject Matter

No claims are allowable.

Any rejections not repeated in this Office Action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
December 13, 2002

DAVID GUZO
PRIMARY EXAMINER